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(54) DERMATOLOGICAL COMPOSITION

(71) We, BRISTOL-MYERS COMPANY, a Corporation organised and existing under the Laws of the State of Delaware, United States of America, of 345 Park Avenue, New York, State of New York, 10022, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a dermatological composition, in particular to a synergistic skin-bleaching composition for use by topical application.

So-called compositions for the bleaching of skin have been known for many years, if not centuries. The prior art contains many references to the use of hydroquinone and its derivatives as agents in, for example, bleaching creams, the most pertinent of which are:

a) U.S. Patent No. 3,060,097, issued October 23, 1962 to a skin-bleaching composition comprising sodium hypochlorite, hydroquinone monobenzyl ether and a "penetrant". Three British Patents No.'s 763,029, 856,431 and 965,869 issued to the same inventor on similar compositions.

b) French Patent No. 1,513,395, issued January 8, 1968 to a skin-bleaching composition comprising hydroquinone monobenzyl ether or a derivative thereof in combination with tyrothricin or a derivative thereof.

c) French Patent No. 1,270,854, issued July 24, 1961 to a skin-bleaching composition comprising hydroquinone benzyl ether (l'ether de benzylhydroquinone) and an antioxidant. The product may be formulated to contain vitamins, amino acids, cholesterol, etc.

d) United States Patents No.'s 2,274,725 (March 3, 1942), 2,376,884 (May 29, 1945) and 2,377,188 (May 29, 1945) are to sunscreen preparations comprising hydroquinone as the active sun-filter agent. These preparations are stabilized by the addition of certain anti-oxidants.

e) Zschr. Haut-Geschl.-Krkh. *42*, 17: 711—716 reports studies of bleaching the skin using hydroquinone monobenzyl ether. When a subject was found to have sensitive skin, 5% hydroquinone monobenzyl ether and 4% prednisolone was used to prevent or control the contact dermatitis produced by the hydroquinone monobenzyl ether. No mention is made of an improved bleaching effect when the preparation contained prednisolone.

f) Some other articles reporting on skin-bleaching by the use of hydroquinone or its derivatives are:

1. Archives of Dermatology, *84*, No. 1, 131—184 (July 1961).
2. Clinical Medicine, *70*, No. 6, 1111—1114 (June 1963).
3. Clinical Medicine, *73*, No. 3, 87—88 (March 1966).
4. Postgraduate Medicine, *37*, No. 2, 198—201 (February 1965).
5. J. Investigative Medicine, *18*, 119—135 (1952).
6. J. Am. Medical Assoc., *152*, No. 7, 577—582 (June 13, 1953).
7. Dermatologica, *134*, 125—128 (1967).
8. Archives of Dermatology, *93*, No. 5, 589—600 (May 1966).

The above cited art constitutes but a small portion of the prior art but is representative of that deemed most pertinent. None of the above teaches or anticipates the three component synergistic compositions of the present invention.

It has long been desirable in certain skin disorders or diseases to be able to depigment (bleach) the skin to remove certain disfiguring blemishes generally caused by the deposition of excess quantities of melanin. This hyper-pigmentation is generally viewed as cosmetically undesirable or psychologically disabling. Examples of these blemishes would be freckles, senile lentigo, lentigines (liver spots), melasma, contact allergy pigmentation, sunburn pigmentation, post-inflammatory hyperpigmentation due to abrasion, burns, wounds, dermatitis, phototoxic reaction and other similar small, fixed pigmented lesions.

Likewise, it is also desirable to be able to decolorize normally pigmented skin to generally increase "fairness" of appearance and to blend hypopigmented areas into surrounding bleached skin. This is particularly so in the treatment of negroes, brown-skinned people, or generally dark-skinned people suffering from vitiligo.

The compounds hydroquinone, hydroquinone monomethyl ether, hydroquinone monobenzyl ethyl, ammoniated mercury, zinc peroxide, red mercuric oxide, sodium hypochlorite, hydrogen peroxide, mercurous chloride and bichloride of mercury are all known in the literature as bleaching agents of the skin. Only hydroquinone is recognized as a bleaching agent possessing satisfactory qualities.

According to the present invention there is provided a skin-bleaching composition for external application, which composition comprises a bleaching agent which is a hydroquinone or an ether thereof, a skin irritant-exfoliating agent, an anti-inflammatory corticosteroid and a pharmaceutically-cosmetically acceptable vehicle.

The compositions of the present invention can be prepared by mixing together the bleaching agent, skin irritant-exfoliating agent and anti-inflammatory corticosteroid and formulating the mixture in a pharmaceutically-cosmetically acceptable vehicle for external application.

A preferred embodiment of the present invention is a synergistic skin-bleaching composition for external application comprising a bleaching agent selected from hydroquinone, hydroquinone monomethyl ether, hydroquinone monoethyl ether and hydroquinone monobenzyl ether, a skin irritant-exfoliating agent and an anti-inflammatory corticosteroid formulated in a pharmaceutically-cosmetically acceptable vehicle.

Another preferred embodiment is a synergistic skin-bleaching composition for external application comprising 1% to 10% by weight of a bleaching agent selected from hydroquinone, hydroquinone monomethyl ether, hydroquinone monoethyl ether and hydroquinone monobenzyl ether, and 0.025% to 80% by weight of a skin irritant-exfoliating agent and 0.01% to 3.0% by weight of an anti-inflammatory corticosteroid formulated in a pharmaceutically-cosmetically acceptable vehicle.

Another preferred embodiment is a synergistic skin-bleaching composition for external application comprising 1% to 5% by weight of a bleaching agent selected from hydroquinone, hydroquinone monomethyl ether, hydroquinone monoethyl ether and hydroquinone monobenzyl ether, 0.25% to 15% by weight of a skin irritant-exfoliating agent selected from unsaturated fatty acids, esters or salts of C_{10}—C_{22} fatty acids, retinoic acid, oleic acid, arachidonic acid, polyoxyethylene lauryl or myristyl ethers, alkylamines containing 5 to 16 carbon atoms, salicylic acid and benzoic acid, and 0.01% to 3.0% by weight of an antiflammatory corticosteroid selected from hydrocortisone, cortisone, prednisolone, prednisone, dexamethasone, betamethasone, fluocinolone acetonide, triamcinolone, fluocinolone, triamcinolone acetonide, methylprednisolone, fluorometholone, or an ester thereof when chemically possible, formulated in a pharmaceutically-cosmetically acceptable vehicle.

A more preferred embodiment is a synergistic skin-bleaching composition for external application comprising 1% to 5% by weight of hydroquinone, 0.020% to 10% by weight of a skin irritant-exfoliating agent selected from retinoic acid, arachidonic acid, oleic acid, linoleic acid, linolenic acid, sodium lauryl sulfate, dioctyl sodium sulfosuccinate, polyoxyethylene lauryl ether, polyoxyethylene myristyl ether, salicylic acid, benzoic acid, and n-octylamine, and 0.01% to 3% by weight of an anti-inflammatory corticosteroid selected from dexamethasone, betamethasone, fluocinolone, flucinolone acetonide, triamcinolone, hydrocortisone, triamcinolone, acetonide, fluorometholone, or an ester thereof when chemically possible, formulated in a pharmaceutically-cosmetically acceptable vehicle.

A most preferred embodiment is the synergistic skin-bleaching composition for external application comprising about 2% by weight hydroquinone, about 0.05% by weight retinoic acid and about 0.025% by weight fluorometholone formulated in a pharmaceutically-cosmetically acceptable vehicle.

Another most preferred embodiment is the synergistic skin-bleaching composition for external application comprising about 2% by weight hydroquinone, about 0.05% by weight retinoic acid and about 0.025% by weight dexamethasone formulated in a pharmaceutically-cosmetically acceptable vehicle.

Still another most preferred embodiment is the synergistic skin-bleaching composition for external application comprising about 2% hydroquinone by weight, about 0.05% by weight retinoic acid and about 2.5% by weight hydrocortisone or hydrocortisone acetate formulated in a pharmaceutically-cosmetically acceptable vehicle.

The invention includes a method for the cosmetic bleaching of human skin, which method comprises applying to the skin a composition in accordance with the invention.

Hydroquinone, hydroquinone monomethyl ether and hydroquinone monobenzyl ether are all known in the literature as bleaching agents for lightening of the skin. While there is some question as to the mode of action of these agents and treatment is considered an "art" rather than a science, it is generally thought that all of these agents work through the

common intermediate hydroquinone. Additionally, it is known that hydroquinone is the least irritating of these hydroquinones, the ethers generally having the reputation of causing various types of dermatitis. It is also known that the ethers are unpredictable in their bleaching effect and sometimes cause a progression of depigmentation after application has been stopped. Hydroquinone is the agent of choice when a hydroquinone bleaching agent is desired for these reasons.

2% hydroquinone composition is commercially available under the tradename Eldoquin and Eldopaque by Paul Elder & Company. Hydroquinone is reported to be the sole active ingredient.

In our hands, it has been found that a preparation containing only 2% hydroquinone is unpredictable and not always effective. Similar results have been reported in the literature (Clinical Medicine, *73*, No. 3, 87—88 [March 1966]) wherein 35% of those subjects treated showed excellent results, 5% good, 35% fair and 25% poor.

Subsequent investigations to improve these results were undertaken and it has been unexpectedly found that a composition containing hydroquinone, or a derivative thereof, in combination with a skin irritant-exfoliating agent and an anti-inflammatory corticosteroid produced good to excellent results in almost all of the subjects so treated. One must consider these results to be a type of synergism inasmuch as these superior results can not be achieved by any of the individual components alone.

The compositions of the present invention are applied according to the following general regimen; In the case of the formulation of Example 1, the composition was applied two to three times daily to the areas to be bleached. The composition is preferably applied three times a day for two days, then two times a day until irritation (mild inflammation) can be seen. Depending upon the degree of irritation, the composition is applied once or twice a day till depigmentation occurs. Depigmentation usually begins to occur five to twenty-one days after the initial application. Depigmentation is usually complete within six to ten weeks.

In patients with recurrent hyperpigmentation (negroes, other dark-skinned races), depigmentation can be maintained by several applications per week.

The results produced by the application of the above composition are exceptionally good. In almost 100% of the subjects so treated, good to excellent depigmentation was obtained. The results were particularly dramatic in normal negro skin, whereon the skin was bleached white in the majority of subjects so treated.

Generally, similar results can be obtained with any of the formulations of the present inventions, although the frequency of application, the time required for depigmentation and the degree of depigmentation will vary with the components, strength, and pharmaceutical vehicle used.

Following is a description by way of example of compositions in accordance with the invention, the percentages being by weight except where otherwise indicated.

Example 1

Hydroquinone	2%
Retinoic Acid	0.05%
Fluorometholone	0.025%
Fragrance q.s.	
Propylene glycol	
Ethanol (95%) aa q.s. ad 100 ml.	

Finely pulverize the hydroquinone, retinoic acid and fluorometholone and dissolve in about 80 ml. of 50:50 mixture by volume of propylene glycol and ethanol. Add the fragrance and q.s. ad to 100 ml. Mix well and apply to area to be bleached.

Example 2

Substitution in the formula of example 1 for the fluorometholone used therein of 0.025% of dexamethasone produces an equivalent formulation.

Example 3

Hydroquinone	2%
Retinoic acid	0.05%
Fluorometholone	0.025%
Vanishing Cream base q.s. as 100 gm.	

Finely pulverize the hydroquinone, retinoic acid and fluorometholone. Add a small quantity of the vanishing cream base and mix well to obtain a gritless paste. Add additional vanishing cream base to make 100 gm. of product. Mix well and apply.

Example 4

Hydroquinone	2%
Retinoic acid	0.05%
Fluorometholone	0.025%
Emolient lotion q.s. ad 100 ml.	

Finely pulverize the hydroquinone, retinoic acid and fluorometholone. Add a small quantity of the emolient lotion to the powder to make gritless paste. Add sufficient lotion to make 100 ml. Mix well and apply.

Example 5

Hydroquinone	2%
Retinoic acid	0.05%
Hydrocortisone	2.5%
Vanishing cream base q.s. ad 100 gm.	

Prepare as in example 3.

Example 6

Hydroquinone	2%
n-Octylamine	0.5%
Fluorometholone	0.025%
Vanishing cream base q.s. ad 100 gm.	

Finely pulverize the hydroquinone and fluorometholone. Add the n-octylamine and a small quantity of vanishing cream to make a gritless paste. Add sufficient vanishing cream to make 100 gm. Mix well and apply.

Example 7

Hydroquinone	2%
Sodium lauryl sulfate	5%
Fluorometholone	0.025%
Vanishing cream base q.s. ad 100 gm.	

Prepare as in example 3.

Example 8

Hydroquinone	2%
Linoleic acid	50%
Fluorometholone	0.025%
Propylene glycol	
Ethanol (95%) aa q.s. ad 100 ml.	

Prepare as in example 1.

Example 9

Hydroquinone	2%
Linolenic acid	55%
Fluorometholone	0.025%
Propylene glycol	
Ethanol (95%) aa q.s. ad 100 ml.	

Prepare as in example 1.

Example 10

Hydroquinone	2%
Arachidonic Acid	10%
Fluorometholone	0.025%
Propylene glycol	
Ethanol (95%) aa q.s. ad 100 ml.	

Prepare as in example 1.

Example 11

Hydroquinone	2%
Polyoxyethylene lauryl ether	10%
Fluorometholone	0.025%
Propylene glycol	
Ethanol (95%) aa q.s. ad 100 ml.	

Prepare as in example 1.

Example 12

Hydroquinone monobenzyl ether	5%
Retinoic acid	0.05%
Fluorometholone	0.025%
Vanishing cream base q.s. ad 100 gm.	

Prepare as in Example 3.

Example 13

Hydroquinone	5%
Retinoic acid	0.05%
Fluorometholone	0.05%
Vanishing cream base q.s. ad 100 gm.	

Prepare as in Example 3.

The compositions of the above Examples were found to be superior and more effective in the bleaching of human skin than compositions currently on the market or known in the literature.

To prepare a more elegant or stable product, it may be desirable to incorporate fragrances, pigments, preservatives and/or a stabilizer including anti-oxidants, all of which are within the ability of those knowledgeable in the art.

WHAT WE CLAIM IS:—

1. A skin-bleaching composition for external application, which composition comprises a bleaching agent which is hydroquinone or an ether thereof, a skin irritant-exfoliating agent, an anti-inflammatory corticosteroid and a pharmaceutically-cosmetically acceptable vehicle.

2. A composition as claimed in claim 1, wherein the bleaching agent is hydroquinone, hydroquinone monomethyl ether, hydroquinone monoethyl ether or hydroquinone monobenzyl ether.

3. A composition as claimed in claim 1 or 2, wherein the corticosteroid is hydrocortisone, cortisone, prednisolone, prednisone, dexamethasone, betamethasone, fluocinolone acetonide, triamicinolone, fluocinolone, triamcinolone acetonide, methylprednisolone or fluorometholone, or an ester thereof when chemically possible.

4. A composition as claimed in any one of the preceding claims, wherein the skin irritant-exfoliating agent is an unsaturated fatty acid, an ester or salt of a fatty acid having from 10 to 22 carbon atoms, retinoic acid, oleic acid, arachidonic acid, a polyoxyethylene lauryl or myristyl ether, an alkylamine containing 5 to 16 carbon atoms, salicylic acid or benzoic acid.

5. A composition as claimed in claim 4, wherein the skin irritant-exfoliating agent is linoleic acid, linolenic acid, sodium lauryl sulfate, dioctyl sodium sulfosuccinate, or n-octylamine.

6. A composition as claimed in any one of the preceding claims containing from 1% to 10% by weight of bleaching agent.

7. A composition as claimed in claim 6, wherein the proportion of bleaching agent is from 1% to 5% by weight.

8. A composition as claimed in any one of the preceding claims containing from 0.025% to 80% by weight of skin irritant-exfoliating agent.

9. A composition as claimed in claim 8, wherein the proportion of skin irritant-exfoliating agent is from 0.025% to 15% by weight.

10. A composition as claimed in any one of claims 1 to 7 containing from 0.020% to 10% by weight of skin irritant-exfoliating agent.

11. A composition as claimed in any one of the preceding claims containing from 0.01% to 3.0% by weight of anti-inflammatory corticosteroid

12. A composition as claimed in claim 1 containing by weight about 2% hydroquinone, about 0.05% retinoic acid and 0.025% fluorometholone.

13. A composition as claimed in claim 1 containing by weight about 2% hydroquinone, about 0.05% retinoic acid and 0.025% dexamethasone.

14. A composition as claimed in claim 1 containing by weight about 2% hydroquinone, about 0.05% retinoic acid and about 2.5% hydrocortisone or hydrocortisone acetate.

15. A composition as claimed in claim 1 substantially as hereinbefore described in any one of the specific Examples.

16. A method of preparing a composition as claimed in any one of claims 1 to 4, which method comprises mixing together the bleaching agent, the skin irritant-exfoliating agent and the anti-inflammatory corticosteroid, and formulating the mixture in a pharmaceutically-cosmetically acceptable vehicle.

17. A method as claimed in claim 16 and substantially as hereinbefore described in any one of the specific Examples.

18. A method for the cosmetic bleaching of human skin, which method comprises applying to the skin a composition as claimed in any one of claims 1 to 16.

19. A method as claimed in claim 18 substantially as hereinbefore described specifically.

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